

**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
(Case No. 98,164-A24)**

**In the Application of:** )  
 )  
**Andrew A. Wolff** )  
 )  
**Serial No.: To Be Assigned** )  
 )  
**Filing Date: Concurrently Herewith** )  
 )  
**For: Sustained Release Ranolazine** )  
**Formulations** )

**INFORMATION DISCLOSURE STATEMENT**

**Commissioner of Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450**

Dear Sir:

Pursuant to 37 C.F.R. Section 1.97 - 1.99, the Applicant wishes to make the following references of record in the above-identified application. This Information Disclosure Statement is in compliance with the continuing duty of candor as set forth in 37 C.F.R. Section 1.56. Pursuant to 37 C.F.R. §1.98(d), copies of references numbered 1-43 are not provided herewith, since they were previously provided in the parent cases, U.S. Patent Application Serial No. 09/925,871, filed on August 9, 2001; and U.S. Patent Application Serial No. 09/321,522 filed on May 27, 1999 now U.S. Patent No. 6,303,607 issued October 16, 2001. These references are also listed on the enclosed PTO Form 1449.

In the judgment of the undersigned, portions of the listed references may be material to the Examiner's consideration of the presently pending claims. This statement is not a representation that the listed references have effective dates early enough to be "prior art" within the meaning of 35 U.S.C. Section 102 or Section 103.

Applicants do not believe any fee is due with this submission. If this belief be in error and the Patent Office determines that the fee prescribed in the relevant portion of 37 C.F.R. Section 1.97 is applicable, the undersigned attorney by his signature hereby authorizes any such fee to be debited from Deposit Account 13-2490.

## **U. S. PATENTS**

1. MacFarlane, et al., U.S. Patent No. 5,209,933, issued May 11, 1993
2. Kluge, et al., U.S. Patent No. 4,567,264, issued January 28, 1986
3. Samuels, et al., U.S. Patent No. 5,472,707, issued December 5, 1995
4. Dow, et al., U.S. Patent No. 5,506,229, issued April 9, 1996
5. Santus, et al., U.S. Patent No. 5,670,171, issued September 23, 1997

## **FOREIGN PATENT DOCUMENTS**

6. WO Patent No. WO 94/26266, published November 24, 1994

## **OTHER DOCUMENTS**

7. Allely MC, Alps BJ. Prevention of myocardial enzyme release by ranolazine in a primate model of ischaemia with reperfusion. *Br J Pharmacol* 99:5-6, 1990.
8. Jain D, Dasgupta P, Hughes LO, Lahiri A, Raftery EB. Ranolazine (RS-43285): A preliminary study of a new anti-anginal agent with selective effect of ischaemic myocardium. *Eur J Clin Pharmacol* 38:111-114, 1990.
9. Lodge JPA, Lam FT, Perry SL, Giles GR. Ranolazine - a new drug with beneficial effects on renal preservation. *Transplantation* 50:755-759, 1990.
10. Cocco G, Rousseau MF, Bouvy T, Cheron P, Williams G, Detry JM, Pouleur H. Effects of a new metabolic modulator, ranolazine, on exercise tolerance in angina pectoris patients treated with  $\beta$ -blocker or diltiazem. *J Cardiovasc Pharmacol* 20:131-138, 1992.
11. Allely MC, Brown CM, Kenny BA, Kilpatrick AT, Martin A, Spedding M. Modulation of  $\beta_1$ -adrenoceptors in rat left ventricle by ischaemia and acyl carnitines: protection by ranolazine. *J Cardiovasc Pharmacol* 21:869-873, 1993.
12. Clarke B, Spedding M, Patmore L, McCormack JG. Protective effects of ranolazine in guinea-pig hearts during low-flow ischaemia and their association with increases in active pyruvate dehydrogenase. *Br J Pharmacol* 109:748-750, 1993.
13. Black SC, Gralinski MR, McCormack JG, Driscoll EM, Lucchesi BR. Effect of ranolazine on infarct size in a canine model of regional myocardial ischemia/reperfusion. *J Cardiovasc Pharmacol* 24:921-928, 1994.
14. Gralinski MR, Black SC, Kilgor KS, Chou AY, McCormack JG, Lucchesi BR. Cardioprotective effects of ranolazine (RS-43285) in the isolated perfused rabbit heart. *Cardiovascular Research* 28:1231-1237, 1994.
15. Hayashida W, Eyll CV, Rousseau MF, Pouleur H. Effects of ranolazine on left ventricular regional diastolic function in patients with ischemic heart disease. *Cardiovascular Drugs and Therapy* 8:741-747, 1994.

16. Thadani U, Exekowitz M, Fenney L, Chiang YK. Double-blind efficacy and safety study of a novel anti-ischemic agent, ranolazine, versus placebo in patients with chronic stable angina pectoris. *Circulation* 90:726-734, 1994.
17. Herron WJ, Eadie J, Penman AD. Estimation of ranolazine and eleven Phase I metabolites in human plasma by liquid chromatography - atmospheric pressure chemical ionisation mass spectrometry with selected ion monitoring. *Journal of Chromatography A* 712:55-60, 1995.
18. Penman AD, Eadie J, Herron WJ, Reilly MA, Rush WR. The characterization of the metabolites of ranolazine in man by liquid chromatography mass spectrometry. *Rapid Communications in Mass Spectrometry* 9:1418-1430, 1995.
19. Wyatt KM, Skene C, Veitch K, Hue L, McCormack JG. The anti-anginal agent ranolazine is a weak inhibitor of the respiratory complex I, but with greater potency in broken or uncoupled than in coupled mitochondria. *Biochemical Pharmacol* 50:1599-1606, 1995.
20. Allen TJ, Chapman RA. Effects of ranolazine on L-type calcium channel currents in guinea-pig single ventricular myocytes. *Br J Pharmacol* 118:249-254, 1996.
21. Clarke B, Wyatt KM, McCormack JG. Ranolazine increases active pyruvate dehydrogenase in perfused normoxic rat hearts: evidence for an indirect mechanism. *J Mol Cell Cardiol* 28:341-350, 1996.
22. McCormack JG, Barr RL, Wolff AA, Lopaschuk GD. Ranolazine stimulates glucose oxidation in normoxic, ischemic, and reperfused ischemic rat hearts. *Circulation* 93:135-142, 1996.
23. McCormack JG, Baracos VE, Barr R, Lopaschuk GD. Effects of ranolazine on oxidative substrate preference in epitrochlearis muscle. *Am Physiol Society*, 905-910, 1996.
24. Wang JX, et al., "Antianginal effects of ranolazine in various experimental models of angina" *Arzneimittelforschung* 1999 Mar; 49(3): 193-9.
26. Matsumura H., et al. "Protective effects of ranolazine, a novel anti-ischemic drug on the hydrogen peroxide-induced derangements in isolated, perfused rat heart: comparison with dichloroacetate." *Jpn J Pharmacol*. 1998 May; 77(1):31-9.
27. McCormack JG, et al., "Ranolazine; a novel metabolic modulator for the treatment of angina." *Gen Pharmacol*. 1998 May; 30(5): 639-45.
28. Bagger JP, et al., "Effects of ranolazine on ischemic threshold, coronary sinus blood flow, and myocardial metabolism in coronary artery disease." *Cardiovasc Drugs Ther*. 1997 Jul;11(3): 479-84.
29. Aaker A, et al., "Effects of ranolazine on the exercise capacity of rats with chronic heart failure induced by myocardial infarction." *J Cardiovasc Pharmacol*. 1996 Sept; 28(3):353-62.

30. Allely MC, Alps BJ, Kilpatrick AT. The effects of the novel anti-anginal agent RS-43285 on [lactic acid], [K<sup>+</sup>] and pH in a canine model of transient myocardial ischaemia. Biochemical Society Transactions 622<sup>nd</sup> Meeting, Leicester 15:1057-1058, 1987.
31. Alley MC, Alps BJ. The effects of the novel anti-anginal agent ranolazine (I.D.) in a canine model of transient myocardial ischaemia. Br J Pharmacol 93(Suppl):246P, 1988
32. Brown CM, Clarke B, Dye A, Fraser S, Kenny BA, Kilpatrick AT, Patmore L, Spedding M, Whiting RL. Pharmacological profile of ranolazine, a metabolic modulator active in ischaemia. Br J Pharmacol 93(Suppl):248P, 1988.
33. Ferrandon P, Pascall JC, Armstrong JM. Protective effects of the novel anti-ischaemic agent ranolazine (RS-43285) in perfused rat hearts. Br J Pharmacol 93(Suppl):247P, 1988.
34. Pouleur H, Hue L, Harlo BJ, Rousseau MF. Metabolic pathways modulation: a new approach to treat myocardial ischemia? Circulation 80, (Supp II):52, 1989.
35. Ferrandon P, Chaylat C, Armstrong JM. Free radical scavengers fail to increase the protective effects of ranolazine in isolated working rat hearts after ischemia and reperfusion. Eur J Pharmacol 183:328-329, 1990.
36. Ferrandon, P et al. Ranolazine but not allopurinol or dipyridamole reduces the ventricular acidosis and lactate produced by low perfusion flow in isolated rat hearts. Therapie 45:10, 1990.
37. Cocco G, Rousseau MF, Bouvy T, Cheron P, William C, Detry JM, Pouleur H. Effects of a novel metabolic modulator, ranolazine, on exercise tolerance and left ventricular filling dynamics in patients with angina petoris. Eur Heart J 13(Suppl):97, 1992.
38. Rousseau MF, Cocco G, Bouvy T, Cheron P, William GJ, Detry JMR, Pouleur H. Effects of a novel metabolic modulator, ranolazine, on exercise tolerance and left ventricular filling dynamics in patients with angina petoris. Circulation 86(Suppl I):2843, 1992.
39. Rousseau MF, Van Eyll C, Van Mechelen H, Harlow BJ, Pouleur H. Novel metabolic ranolazine selectively improves diastolic function in heart failure. Circulation 86(Suppl):375, 1992.
40. Collins-Nakai RL, Barr R, Humen D, Lopaschuk GD. Ranolazine stimulates glucose oxidation in isolated working rat hearts. Can J Cardiol 9(Suppl E):104E, 1993.
41. Rousseau MR, Visser FG, Bax JJ, Dubrey S, Cocco G, Pouleur H, Harris SA, Wolff AA. Ranolazine: anti-anginal therapy with a novel mechanism: placebo controlled comparison versus atenolol. Eur Heart J 15 (Suppl I):95, 1994.  
(note: the data in this abstract are from the correct analysis.)

42. Rousseau MR, Visser FG, Bax JJ, Noble MIM, Dubrey S, Cocco G, Pasteuning WH, Williams G, Dodds P, Pouleur H. Is modulation of myocardial metabolism as effective as  $\beta$ -blockade in exercise-induced angina? J Am Coll Cardiol 23 (Supp I):268A, 1994.  
*(note: the data in the abstract are not from the final analysis.)*
43. Smith WB, Chrysant S, Garland WT, Parker TS, Walpole HT, Mokatrini A, Gennevois D, Pepine CJ. A multicenter controlled trial of a novel metabolic active compound (ranolazine) in chronic stable angina patients. J Am Coll Cardio 24A, February 1995.

Respectfully submitted,  
**McDonnell Boehnen Hulbert & Berghoff**

Date: July 7, 2003

By: 

A. Blair Hughes  
Reg. No. 32,901

FORM PTO-1449  
(Rev. 2-32)

U.S. Department of Commerce  
Patent and Trademark Office

INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT  
(Use several sheets if necessary)

Atty. Docket No.

98,164-A24

Serial No.

To Be Assigned

Applicant:

Wolff

Filing Date:

Concurrently Herewith

Group:

U.S. PATENT DOCUMENTS

Examiner Initial	Document Number	Date	Name	Class	Subclasses	Filing Date if Appropriate
	5,209,933	5/11/93	MacFarlane et al.			
	4,567,264	1/28/96	Kluge et al.			
	5,472,707	12/5/95	Samuels et al.			
	5,506,229	4/9/96	Dow et al.			
	5,670,171	9/23/97	Santus et al.			

FOREIGN PATENT DOCUMENTS

	Document Number	Date	Country	Class	Subclass	Translation	
						Yes	No
	WO 94/26266	11/24/94					

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc).

		Allely MC, Alps BJ. Prevention of myocardial enzyme release by ranolazine in a primate model of ischaemia with reperfusion. Br J Pharmacol 99:5-6, 1990.
		Jain D, Dasgupta P, Hughes LO, Lahiri A, Raftery EB. Ranolazine (RS-43285): A preliminary study of a new anti-anginal agent with selective effect of ischaemic myocardium. Eur J Clin Pharmacol 38:111-114, 1990.
EXAMINER		
DATE CONSIDERED		

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication.

<b>FORM PTO-1449</b> (Rev. 2-32)  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> (Use several sheets if necessary)	<b>U.S. Department of Commerce</b> <b>Patent and Trademark Office</b>		<b>Atty. Docket No.</b>  98,164-A24	<b>Serial No.</b>  To Be Assigned
	<b>Applicant:</b>  Wolff			
	<b>Filing Date:</b> Currently Herewith		<b>Group:</b>	

**OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc).**

			Lodge JPA, Lam FT, Perry SL, Giles GR. Ranolazine - a new drug with beneficial effects on renal preservation. Transplantation 50:755-759, 1990.
			Cocco G, Rousseau MF, Bouvy T, Cheron P, Williams G, Detry JM, Pouleur H. Effects of a new metabolic modulator, ranolazine, on exercise tolerance in angina pectoris patients treated with $\beta$ -blocker or diltiazem. J Cardiovasc Pharmacol 20:131-138, 1992
			Allely MC, Brown CM, Kenny BA, Kilpatrick AT, Martin A, Spedding M. Modulation of $\alpha_1$ -adrenoceptors in rat left ventricle by ischaemia and acyl carnitines: protection by ranolazine. J Cardiovasc Pharmacol 21:869-873, 1993
			Clarke B, Spedding M, Patmore L, McCormack JG. Protective effects of ranolazine in guinea-pig hearts during low-flow ischaemia and their association with increases in active pyruvate dehydrogenase. Br J Pharmacol 109:748-750, 1993
			Black SC, Gralinski MR, McCormack JG, Driscoll EM, Lucchesi BR. Effect of ranolazine on infarct size in a canine model of regional myocardial ischemia/reperfusion. J Cardiovasc Pharmacol 24:921-928, 1994.
			Gralinski MR, Black SC, Kilgor KS, Chou AY, McCormack JG, Lucchesi BR. Cardioprotective effects of ranolazine (RS-43285) in the isolated perfused rabbit heart. Cardiovascular Research 28:1231-1237, 1994
			Hayashida W, Eyll CV, Rousseau MF, Pouleur H. Effects of ranolazine on left ventricular regional diastolic function in patients with ischemic heart disease. Cardiovascular Drugs and Therapy 8:741-747, 1994.
			Thadani U, Exekowitz M, Fenney L, Chiang YK. Double-blind efficacy and safety study of a novel anti-ischemic agent, ranolazine, versus placebo in patients with chronic stable angina pectoris. Circulation 90:726-734, 1994
			Herron WJ, Eadie J, Penman AD. Estimation of ranolazine and eleven Phase I metabolites in human plasma by liquid chromatography - atmospheric pressure chemical ionisation mass spectrometry with selected -ion monitoring. Journal of Chromatography A 712:55-60, 1995
			Penman AD, Eadie J, Herron WJ, Reilly MA, Rush WR. The characterization of the metabolites of ranolazine in man by liquid chromatography mass spectrometry. Rapid Communications in Mass Spectrometry 9:1418-1430, 1995
			Wyatt KM, Skene C, Veitch K, Hue L, McCormack JG. The anti-anginal agent ranolazine is a weak inhibitor of the respiratory complex I, but with greater potency in broken or uncoupled than in coupled mitochondria. Biochemical Pharmacol 50:1599-1606, 1995
			Allen TJ, Chapman RA. Effects of ranolazine on L-type calcium channel currents in guinea-pig single ventricular myocytes. Br J Pharmacol 118:249-254, 1996
			Clarke B, Wyatt KM, McCormack JG. Ranolazine increases active pyruvate dehydrogenase in perfused normoxic rat hearts: evidence for an indirect mechanism. J Mol Cell Cardiol 28:341-350, 1996.
			McCormack JG, Barr RL, Wolff AA, Lopaschuk GD. Ranolazine stimulates glucose oxidation in normoxic, ischemic, and reperfused ischemic rat hearts. Circulation 93:135-142, 1996
EXAMINER			DATE CONSIDERED

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication.

<b>FORM PTO-1449</b> <b>(Rev. 2-32)</b>	<b>U.S. Department of Commerce</b> <b>Patent and Trademark Office</b>	<b>Atty. Docket No.</b>	<b>Serial No.</b>
<b>INFORMATION DISCLOSURE</b> <b>STATEMENT BY APPLICANT</b> (Use several sheets if necessary)		98,164-A24	To Be Assigned
		<b>Applicant:</b>	
		Wolff	
		<b>Filing Date:</b>	<b>Group:</b>
		Currently Herewith	

**OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc).**

		McCormack JG, Baracos VE, Barr R, Lopaschuk GD. Effects of ranolazine on oxidative substrate preference in epitrochlearis muscle. Am Physiol Society, 905-910, 1996.
		Wang JX, et al., "Antianginal effects of ranolazine in various experimental models of angina." Arzeinmittelforschung 1999 Mar; 49(3): 193-9
		Matsumura H., et al. "Protective effects of ranolazine, a novel anti-ischemic drug on the hydrogen peroxide-induced derangements in isolated, perfused rate heart: comparison with dichloroacetate." Jpn J Pharmacol. 1998 May; 77(1)31-9
		McCormack JG, et al., "Ranolazine; a novel metabolic modulator for the treatment of angina." Gen Pharmacol. 1998 May; 30(5): 639-45.
		Bagger JP, et al., "Effects of ranolazine on ischemic threshold, coronary sinus blood flow, and myocardial metabolism in coronary artery disease." Cardiovasc Drugs Ther. 1997 Jul;11(3): 479-84.
		Aaker A, et al., "Effects of ranolazine on the exercise capacity of rats with chronic heart failure induced by myocardial infarction." J Cardiovasc Pharmacol. 1996 Sept; 28(3):353-62.

		Allely MC, Alps BJ, Kilpatrick AT. The effects of the novel anti-anginal agent RS-43285 on [lactic acid], [K <sup>+</sup> ] and pH in a canine model of transient myocardial ischaemia. Biochemical Society Transactions 622 <sup>nd</sup> Meeting, Leicester 15:1057-1058, 1987
		Alley MC, Alps BJ. The effects of the novel anti-anginal agent ranolazine (I.D.) in a canine model of transient myocardial ischaemia. Br J Pharmacol 93(Suppl):246P, 1988
		Brown CM, Clarke B, Dye A, Fraser S, Kenny BA, Kilpatrick AT, Patmore L, Spedding M, Whiting RL. Pharmacological profile of ranolazine, a metabolic modulator active in ischaemia. Br J Pharamacol 93(Suppl):248P, 1988
		Ferrandon P, Pascall JC, Armstrong JM. Protective effects of the novel anti-ischaemic agent ranolazine (RS-43285) in perfused rat hearts. Br J Pharmacol 93(Suppl):247P, 1988
		Pouleur H, Hue L, Harlo BJ, Rousseau MF. Metabolic pathways modulation: a new approach to treat myocardial ischemia? Circulation 80, (Supp II):52, 1989
		Ferrandon P, Chaylat C, Armstron JM. Free radical scavengers fail to increase the protective effects of ranolazine in isolated working rat hearts after ischemia and reperfusion. Eur J Pharmacol 183:328-329, 1990
EXAMINER		DATE CONSIDERED

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication.



FORM PTO-1449  
(Rev. 2-32)

U.S. Department of Commerce  
Patent and Trademark Office

Atty. Docket No.

98,164-A24

Serial No.

To Be Assigned

INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT

(Use several sheets if necessary)

Applicant:

Wolff

Filing Date:

Concurrently Herewith

Group:

ABSTRACTS

			Ferrandon, P et al. Ranolazine but not allopurinol or dipyridamole reduces the ventricular acidosis and lactate produced by low perfusion flow in isolated rat hearts. Therapie 45:10, 1990
			Cocco G, Rousseau MF, Bouvy T, Cheron P, William C, Detry JM, Pouleur H. Effects of a novel metabolic modulator, ranolazine, on exercise tolerance and left ventricular filling dynamics in patients with angina pectoris. Eur Heart J 13(Supp):97, 1992
			Rousseau MF, Cocco G, Bouvy T, Cheron P, William GJ, Detry JMR, Pouleur H. Effects of a novel metabolic modulator, ranolazine, on exercise tolerance and left ventricular filling dynamics in patients with angina pectoris. Circulation 86(Supp I):2843, 1992.
			Rousseau MF, Van Eyll C, Van Mechelen H, Harlow BJ, Pouleur H. Novel metabolic ranolazine selectively improves diastolic function in heart failure. Circulation 86(Suppl):375, 1992.
			Collins-Nakai RL, Barr R, Humen D, Lopaschuk GD. Ranolazine stimulates glucose oxidation in isolated working rat hearts. Can J Cardiol 9(Supp E):104E, 1993
			Rousseau MR, Visser FG, Bax JJ, Dubrey S, Cocco G, Pouleur H, Harris SA, Wolff AA. Ranolazine: anti-anginal therapy with a novel mechanism: placebo controlled comparison versus atenolol. Eur Heart J 15 (Suppl I):95, 1994.
			Rousseau MR, Visser FG, Bax JJ, Noble MIM, Dubrey S, Cocco G, Pasteuning WH, Williams G, Dodds P, Pouleur H. Is modulation of myocardial metabolism as effective as $\beta$ -blockade in exercise-induced angina? J Am Coll Cardiol 23 (Supp I):268A, 1994
			Smith WB, Chrysant S, Garland WT, Parker TS, Walpole HT, Mokatrin A, Gennevois D, Pepine CJ. A multicenter controlled trial of a novel metabolic active compound (ranolazine) in chronic stable angina patients. J Am Coll Cardio 24A, February 1995
EXAMINER			DATE CONSIDERED

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication.